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EXPRESSION OF PROGRAMMED CELL DEATH RECEPTOR IN ENDOMETRIAL CANCER PATIENTS WITH METABOLIC DISORDERS

Aim. To study the expression of the programmed cell death receptor (PD-1) and its ligand (PD-L1) by immunocompetent cells in endometrial cancer patients with metabolic disorders. **Materials and Methods.** Populations and subpopulations of lymphocytes were analyzed by flow cytometry. Antibodies against CD279 were used to detect PD-1 on the $CD4^+$ and $CD8^+$ T cells. Antibodies against CD14 and CD274 were used to detect PD-L1 on monocytes. **Results.** In patients with severe metabolic disorders, the expression of PD-1 on $CD8^+$ and $CD4^+$ lymphocytes and the expression of the corresponding PD-L1 on $CD14^+$ cells before treatment and after radiation therapy were higher than in the control group. **Conclusion.** The increased expression of PD-1 and PD-L1 receptors by immunocompetent cells can be considered a new prognostic marker in endometrial cancer patients with morbid obesity.

Keywords: endometrial cancer, programmed cell death receptor, metabolic disorders, population and subpopulation composition of lymphocytes.

According to statistics, endometrial cancer (EC) ranks first among the malignant neoplasms of the female genital organs and occupies the 7th place in cancer-related mortality. In 2019, 324,605 new cases of EC were registered in the world, 53% of which were registered in developed countries. In Ukraine, EC incidence in 2020 was 29.4 per 100 thousand population [1, 2].

The main methods of EC treatment are surgery and radiation therapy, which are accompanied by significant immunoendocrine shifts.

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The development of most chronic diseases including cancer is closely linked to metabolic disorders. There is substantiated evidence of a link between the metabolic syndrome (MS) and the increased risk of uterine cancer in postmenopausal women [3, 4].

A vast proportion of cancer patients have metabolic disorders associated with an increased risk of EC development and resistance to treatment affecting the outcomes [5].

The adverse effects of MS on the complications and outcomes of antitumor treatment can be caused by both direct metabolic disorders and closely related immune disorders. The increase in inflammatory mediators induced by metabolic disorders may mediate these adverse effects and the disease outcome [6].

The programmed cell death-1 protein (PD-1) is present on the surface of T cells while its immunosuppressive ligand PD-L1 is expressed on cancer cells. The analysis of subpopulations of lymphocytes expressing immunosuppressive molecules PD-1 and PD-L1 becomes a fascinating field of investigation as the activation of the PD1/PD-L1 signaling pathway is associated with the deterioration of antitumor immunity [7, 8] and is considered an unfavorable prognostic factor for cancer patients [9—11]. The results of the current investigations demonstrate that the evaluation of the expression levels of PD-1 and PD-L1 molecules appears to be a potential biomarker for predicting the outcome of cancer treatment.

The aim of our work was to study the changes in the expression of PD-1 and its ligand PD-L1 by immunocompetent cells in EC patients with obesity as one of the MS signs.

Materials and Methods

The study included patients treated at the State Institution "Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine" (Kharkiv, Ukraine) in 2018—2020. All patients gave informed consent to the use of clinical samples for research purposes. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964—2008), European Community Directive 86/609 on human participation in biomedical research, and Order No. 690 from 23.09.2009 of the Ministry of Health of Ukraine.

45 patients with EC stage 1b (T1bN0M0) were included in the study. In all patients, endometrial adenocarcinoma of a moderate differentiation grade (G2) was histologically determined. Women aged 51 to 60 years predominated. All patients underwent a course of remote gamma therapy on a linear accelerator Clinac 600C (Varian Medical Systems, USA). The total focal dose was 40—45 Gy. Examinations were performed before and after a course of remote gamma therapy. The changes in metabolic and immunological parameters were described in more detail in our previous article [12].

Peripheral blood was used to analyze the cells of the immune system. Venous blood sampling was carried out in vacuum tubes containing a salt of ethylenediaminetetraacetic acid (K2-EDTA, K3-EDTA). To remove erythrocytes, sample preparation was performed according to the no-wash technology using an OptiLyse C lysin solution (Beckman Coulter, USA). Populations and the subpopulations of lymphocytes were analyzed by flow cytometry on an FC-500 cytometer using monoclonal antibodies from Beckman Coulter (USA). To correctly exclude from the analysis zone all particles that did not correspond in size and granularity to intact lymphocytes, the necessary logical restrictions were introduced into the histograms of particle distribution by small-angle and side light scattering and a pan-leukocyte marker CD45 (clone J33). The absolute number of cells was determined in a two-platform device (using the results of the

RT-7600 hematology analyzer (Rayto, China)). Mathematical processing of cytometric data was performed using the CXP v. 2.2 programs (Beckman Coulter, USA). The analysis results are presented as percentiles with a significance of 0.05. Antibodies to CD3 (clone UCHT1), CD8 (clone B9.11), and CD279 (clone PD1.3) were used to detect PD-1 on T cells with the $CD3^{+}CD8^{+}$ phenotype; antibodies against CD3 (clone UCHT1), CD4 (clone 13B8.2), and CD279 (clone PD1.3) were used on T cells with the $CD3^{+}CD4^{+}$ phenotype. Antibodies against CD14 (clone RM052) and CD274 (clone PDL1.3.1) were used to detect PD-L1 on monocytes with the $CD14^{+}CD274^{+}$ phenotype.

The leptin level was measured using a set of reagents for enzyme-linked immunosorbent assay «Leptin Sandwich ELISA» (DRG Instruments GmbH, Germany). Analysis of the serum level of C-reactive protein was performed on an automatic biochemical analyzer «RESPONS 910» (DiaSys Diagnostic Systems GmbH, Germany). The serum level of insulin was determined using a set of reagents for enzyme-linked immunosorbent assay “DRG Insulin ELISA (EIA-2935)” (DRG Instruments GmbH, Germany).

Statistical analysis was performed using the software package Statistica 13.3 EN (StatSoft, USA). Indicators had a distribution that was different from normal, descriptive statistics are given as the median, lower, and upper quartiles — Me (Q25; Q75). Quantitative indicators in the groups were compared using Student’s *t*-test (for the normal distribution of traits) and the Mann — Whitney U-test (for the distribution of traits other than normal). The Pearson correlation coefficient (r) was calculated. The difference at $p < 0.05$ was considered statistically significant.

Results and Discussion

Upon the anthropometric examination, BMI was calculated by Quetelet index according to the formula: weight (kg) : $(\text{height})^2$ (m^2). According to BMI, patients were divided into groups. Patients with normal weight (BMI from 20.0 to 24.9 kg/m^2) formed the control group (C); patients with class I obesity (BMI = 30.0—34.9), patients with class II obesity (BMI = 35.0—39.9), and patients with class III obesity (BMI > 40) form groups I, II, and III, respectively. Among EC patients, 18% had a normal weight, class I obesity was found in 39% of patients, class II in 18% of patients, and class III in 25% of patients.

The lymphocyte subpopulations differed between the study groups of patients before treatment (Table 1). In patients of group III, a slightly lower level of the relative number of $CD3^{+}$ lymphocytes was observed while in groups I and II it was close to that in the control group.

Prior to the treatment, EC patients with obesity (groups I, II, and III) had a higher proportion of T cells expressing PD-1 than patients with normal weight (group C) (Table 1). This may indicate a predominance of negative T-cell regulation in obese patients.

PD-1 plays an important role in the negative regulation of the effector functions of T-helpers and cytotoxic T-lymphocytes [13, 14]. This molecule is poorly represented on the surface of the resting T cells, but a few hours after stimulation, the level of its expression increases sharply [8]. The increased level of PD-1 is closely associated with a decrease in the ability of $CD3^{+}CD8^{+}$ cells to exhibit cytolytic properties.

After radiation therapy, patients with metabolic disorders (groups I, II, and III) had higher median $PD\text{-}1^{+}$-expressing T cells than patients with normal weight (group C) (Table 2). Our data are in agreement with the work of Ribas [14] who observed an increase in the expression of PD-1 on T cells of cancer patients. Thus, higher expression of PD-1 on T cells is associated with inhibition of the effector phase of T cell responses and reduced antitumor activity. More recently, the PD-1 expression on $CD4^{+}CD8^{+}$ T lymphocytes has been reported to be signifi-

Table 1. **Immunological parameters in EC patients before treatment**

Index	Control group (C)	Group I	Group II	Group III
	Me (Q_{25} – Q_{75})			
$CD3^+$, %	70.3 (65.3—78.7)	71.5 (66.3—78.7)	68.8 (66.3—72.7)	66.1 (59.4—73.0)
$CD3^+$, $\cdot 10^9$/L	1.0 (0.9—1.1)	1.3 (1.0—1.4)	1.2 (1.1—1.4)	1.4 (1.2—1.7) *
$CD3^+CD4^+$, %	38.1 (33.9—41.4)	42.7 (40.0—50.3)	45.4 (41.9—49.7) *	48.5 (43.6—56.0) *
$CD3^+CD4^+$, $\cdot 10^9$/L	0.7 (0.6—0.8)	0.8 (0.6—0.9)	0.8 (0.7—0.9)	0.9 (0.8—1.1) *
$CD3^+CD8^+$, %	15.1 (10.8—25.9)	24.1 (19.0—29.9)	21.9 (18.4—26.6)	23.3 (19.6—30.3)
$CD3^+CD8^+$, $\cdot 10^9$/L	0.3 (0.1—0.7)	0.4 (0.3—0.5)	0.4 (0.3—0.5)	0.5 (0.3—0.6)
IRI (CD4/CD8)	2.9 (1.3—4.1)	1.7 (1.3—2.7)	2.2 (1.5—2.6)	2.8 (1.5—2.8)
$CD4^+CD279^+$, %	4.7 (3.2—4.8)	10.2 (8.2—11.9) *	11.9 (10.6—17.0) *	26.2 (19.9—30.9) *
$CD4^+CD279^+$, $\cdot 10^9$/L	0.04 (0.02—0.05)	0.43 (0.34—0.55) *	0.28 (0.21—0.33) *	0.34 (0.21—0.41) *
$CD8^+CD279^+$, %	2.1 (1.1—3.1)	12.5 (9.7—13.8) *	13.2 (12.5—14.2) *	17.8 (15.7—19.0) *
$CD8^+CD279^+$, $\cdot 10^9$/L	0.04 (0.01—0.06)	0.06 (0.05—0.07)	0.19 (0.16—0.28) *	0.21 (0.16—0.29) *
$CD14^+CD274^+$, %	0.10 (0.07—0.011)	0.21 (0.18—0.32) *	0.25 (0.12—0.38) *	0.45 (0.34—0.51) *
$CD14^+CD274^+$, $\cdot 10^9$/L	0.0006 (0.0005—0.0030)	0.001 (0.001—0.002) *	0.004 (0.003—0.005)	0.008 (0.004—0.009) *

Note: * $p < 0.05$ as compared with the control group; IRI — immunoregulatory index.

Table 2. **Immunological parameters in EC patients after treatment**

Index	Control group (C)	Group I	Group II	Group III
	Me (Q_{25} – Q_{75})			
$CD3^+$, %	76.1 (55.6—79.7)	73.1 (70.6—83.1)	79.8 (75.5—83.4)	83.1 (76.5—84.5)
$CD3^+$, $\cdot 10^9$/L	0.2 (0.1—0.3)	0.3 (0.3—0.4)	0.3 (0.2—0.45)	0.4 (0.3—0.6)
$CD3^+CD4^+$, %	36.2 (31.7—43.0)	47.4 (40.7—50.2)	52.8 (50.0—55.0)	57.5 (49.1—63.3)
$CD3^+CD4^+$, $\cdot 10^9$/L	0.2 (0.1—0.2)	0.2 (0.2—0.3)	0.1 (0.1—0.2)	0.2 (0.2—0.3)
$CD3^+CD8^+$, %	27.3 (24.3—33.5)	25.2 (18.8—34.4)	28.0 (11.7—33.4)	26.7 (19.3—34.8)
$CD3^+CD8^+$, $\cdot 10^9$/L	0.1 (0.1—0.2)	0.1 (0.1—1.2)	0.1 (0.01—0.2)	0.1 (0.1—0.2)
IRI (CD4/CD8)	1.2 (0.9—1.3)	2.1 (1.2—2.5)	2.8 (2.2—3.4) *	3.1 (2.7—3.2) *
$CD4^+CD279^+$, %	4.0 (3.3—5.2)	5.1 (3.6—5.5)	6.9 (5.6—8.5) *	12.0 (10.5—13.1) *
$CD4^+CD279^+$, $\cdot 10^9$/L	0.05 (0.04—0.06)	0.06 (0.04—0.07)	0.1 (0.08—0.2) *	0.2 (0.1—0.3) *
$CD8^+CD279^+$, %	2.7 (1.9—3.0)	3.0 (1.9—3.5)	3.3 (3.0—3.5) *	4.0 (3.8—4.6) *
$CD8^+CD279^+$, $\cdot 10^9$/L	0.03 (0.02—0.04)	0.03 (0.01—0.06)	0.06 (0.04—0.08) *	0.08 (0.06—0.11) *
$CD14^+CD274^+$, %	0.25 (0.18—0.27)	0.74 (0.65—0.82) *	0.58 (0.46—0.63) *	0.68 (0.54—0.72) *
$CD14^+CD274^+$, $\cdot 10^9$/L	0.002 (0.001—0.004)	0.01 (0.01—0.02)	0.03 (0.01—0.05)	0.06 (0.04—0.08) *

Note: * $p < 0.05$ as compared with the control group; IRI — immunoregulatory index.

Table 3. **Correlation between metabolic and immunological parameters after radiation treatment**

Index	Insulin		CRP		Leptin	
	r	*p*	r	*p*	r	*p*
$CD3^+CD8^+CD279^+$, $\cdot 10^9$/L	0.303	0.00405	–0.406	0.00016	0.610	0.00013
$CD3^+CD4^+CD279^+$, $\cdot 10^9$/L	0.511	0.00032	–0.328	0.00034	0.434	0.00033
$CD14^+CD274^+$,$\cdot 10^9$/L	0.284	0.00501	0.350	0.00021	0.328	0.00451

cantly higher in patients with chronic lymphocytic leukemia [15].

PD-L1 is widely expressed by hematopoietic (T and B cells, monocytes, macrophages, dendritic cells, myeloid suppressor cells, etc.) and non-hematological cells (endothelial, epithelial, muscle, trophoblast cells, Langerhans cells of the pancreas, etc.). The interaction of PD-L1 with its receptor results in cell inactivation and/or apoptosis. This mechanism plays an important role in the regulation of the immune response [16]. It is also assumed that this mechanism is widely used by tumor cells to evade the immune control.

In all groups of EC patients with obesity after radiation therapy, higher median relative and absolute counts of $CD14^+PD\text{-}L1^+$ cells were observed (Table 2).

It is known that the interaction between the functional partners PD-1 and PD-L1 provides suppression of the immune response, especially in cancer [17, 18]. Dysregulation of the PD-1/PD-L1/2 pathways has been reported to be associated with an unfavorable prognosis including the treatment resistance and rapid disease progression [19, 20].

The correlation analysis after radiation treatment revealed relationships between the levels of insulin, C-reactive protein, leptin, and $CD8^+PD\text{-}1^+$, $CD4^+PD\text{-}1^+$ lymphocyte counts and the $CD14^+PD\text{-}L1^+$ cell counts (Table 3).

In recent years, studies have shown a role of the leptin/leptin receptor dysregulation in the development of different cancers including EC, mainly through the JAK/STAT signaling pathway, which modulates ERK1/2 signaling, the expression of anti-apoptotic proteins (such as XIAP), inflammatory proteins (TNF-α, IL-6) and angiogenic factors, and hypoxia-inducible factor-1α [21, 22]. The involvement of leptin in the development of drug resistance has been reported as well [23, 24].

The correlation analysis revealed a positive relationship between the $CD3^+CD8^+CD279^+$ and BMI in patients with endometrial cancer ($r = 0.963$; $p = 0.00000001$). Therefore, in patients with pronounced metabolic disorders, systemic changes occur, which can contribute to the development and progression of cancer as well as to the development of resistance to anticancer treatment.

To sum up, we have found that in EC patients with severe metabolic disorders (class III obesity), the expression of CD-1 suppressor receptors on $CD8^+$ and $CD4^+$ lymphocytes and the expression of the corresponding PD-L1 ligand on $CD14^+$ cells before treatment and after radiation therapy was higher than in the control group. The increased expression of PD-1 and PD-L1 by immunocompetent cells can be suggested as a new prognostic marker in EC patients with morbid obesity.

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ЕКСПРЕСІЯ РЕЦЕПТОРА ПРОГРАМОВАНОЇ КЛІТИННОЇ ЗАГИБЕЛІ У ХВОРИХ НА РАК ЕНДОМЕТРІЯ З МЕТАБОЛІЧНИМИ ПОРУШЕННЯМИ

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Мета. Вивчити зміни експресії рецептора програмованої клітинної смерті (PD1) та його ліганду (PD-L1) імунокомпетентними клітинами у хворих на рак ендометрія з ожирінням як однієї з ознак метаболічного синдрому. **Матеріали та методи.** Популяційний і субпопуляційний склад лімфоцитів визначали методом проточної цитометрії. Антитіла проти CD279 використовували для виявлення PD1 на $CD4^+$ та $CD8^+$ Т-клітинах. Антитіла проти CD14 та CD274 використовували для виявлення PD-L1 на моноцитах. **Результати.** Встановлено, що у хворих із тяжкими метаболічними порушеннями експресія PD1 на $CD4^+$ та $CD8^+$ Т-клітинах та експресія відповідного ліганду *PDL-1* на $CD14^+$ клітинах до лікування та після променевої терапії були вищими, ніж у контрольній групі. **Висновки.** Підвищену експресію PD-1 та PD-L1 імунокомпетентними клітинами можна розглядати як новий прогностичний маркер у хворих на рак ендометрія з морбідним ожирінням.

Ключові слова: рак ендометрія, рецептор програмованої клітинної смерті (PD1), ліганд рецептора запрограмованої клітинної смерті (PD-L1), популяційний та субпопуляційний склад лімфоцитів.